



Commentary

USP–NF 2023 Issue 2

February 1, 2023

In accordance with USP’s *Rules and Procedures of the Council of Experts (“Rules”)*, and except as provided in Section 9.02 *Accelerated Revision Processes*, USP publishes proposed revisions to the *United States Pharmacopeia and the National Formulary (USP–NF)* for public review and comment in the *Pharmacopeial Forum (PF)*, USP’s free bimonthly journal for public notice and comment. After comments are considered and incorporated as the Expert Committee (EC) deems appropriate, the proposal may advance to official status or be re-published in *PF* for further notice and comment, in accordance with the Rules. In cases when proposals advance to official status, a summary of comments received and the appropriate Expert Committee’s responses, as well as Expert Committee-initiated changes, are published in the Proposal Status/Commentary section of USP.NF.com at the time the official revision is published.

The *Commentary* is not part of the official text and is not intended to be enforceable by regulatory authorities. Rather, it explains the basis of Expert Committees’ responses to public comments on proposed revisions. If there is a difference or conflict between the contents of the *Commentary* and the official text, the official text prevails.

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Comments were received for the following when they were proposed in Pharmacopeial Forum:

Test Solutions

[Starch TS](#)

General Chapters

[<3> Topical and Transdermal Drug Products - Product Quality Tests](#)

[<5> Inhalation and Nasal Drug Products General Information and Product Quality Tests](#)

[<313> Molecular Weight and Polymer Chain Length Determination for Polypropylene Glycol Fatty Ethers](#)

[<1083> Supplier Qualification](#)

[<1212> Probe Tack Test](#)

Monographs

[Amlodipine Besylate](#)

[Bifidobacterium Bifidum](#)

[Bifidobacterium Longum subsp Longum](#)

[Black Cumin Seed Thymoquinone Oil](#)

[Calcium Ascorbate](#)

[Cevimeline Hydrochloride](#)

[Choline Chloride](#)

[Clonidine Hydrochloride Tablets](#)

[Dobutamine Hydrochloride](#)

[Emulsifying Wax](#)

[Hydroxychloroquine Sulfate Compounded Oral Suspension](#)

[Ipratropium Bromide](#)

[Mesalamine Extended-Release Capsules](#)

[Methylene Blue](#)

[Micafungin For Injection](#)

[Micafungin Sodium](#)

[Morphine Sulfate Compounded Oral Solution](#)

[Neomycin Sulfate](#)

[Oxymorphone Hydrochloride](#)

[Polyethylene Glycol 30 Dipolyhydroxystearate 5](#)

[Polyethylene Glycol 12 Cetostearyl Ether](#)

[Prasugrel Hydrochloride](#)

[Roflumilast](#)

[Sildenafil Injection](#)

[Silver Nitrate](#)

[Sodium Ascorbate](#)

[Sodium Chloride Compounded Injection](#)

[Sodium Iodide I 123 Solution](#)

[Sodium Nitrite](#)

[Sodium Picosulfate](#)

[Triazolam Tablets](#)

[Triclabendazole](#)

[Zinc Chloride](#)

No comments were received for the following proposals:

Monographs

Compound Undecylenic Acid Ointment
Corticotropin Injection
Corticotropin For Injection
Dong Quai Root
Dong Quai Root Powder
Doxycycline For Oral Suspension
Ensulizole
Guanidine Hydrochloride
Isosorbide Dinitrate Extended-Release Tablets
Metoprolol Succinate Extended-Release Tablets
Mycophenolate Mofetil Capsules
Mycophenolate Mofetil Tablets
Norflurane
Pantoprazole Sodium Delayed-Release Tablets
Sichuan Lovage Rhizome
Sichuan Lovage Rhizome Powder
Sodium Nitrite Injection
Terminalia Chebula Fruit
Terminalia Chebula Fruit Dry Extract
Terminalia Chebula Fruit Powder
Tetracycline Hydrochloride Ointment
Tetracycline Hydrochloride Tablets
Valine Compounded Oral Solution

Test Solutions

Documentary Standard: Starch TS

Expert Committee: USP Headquarters

Commenters: 2

Comment Summary #1: A commenter recommended adding sufficient boiling water to solubilize the starch. In addition, they recommended reducing the concentration of the iodine used in the *Test for Sensitivity* to facilitate the visualization of the endpoint.

Response: Comments incorporated. The preparation of all Starch TS solutions and the conditions of the *Test for Sensitivity* were revised to provide clarity on the amount of water used to prepare the paste from 5 mL to 50 mL.

Response: Comment not incorporated. The 5 mL volume of water is enough to prepare the paste. The solubilization will happen with the addition of the boiling water

General Chapters

General Chapter/Section(s): <3> Topical and Transdermal Drug Products – Product Quality Tests / Multiple Sections

Expert Committee(s): General Chapters – Dosage Forms

No. of Commenters: 8

Comment Summary #1: Under *Microbiological Quality*, the commenter suggested specifying that <60> is only required for aqueous, non-sterile products.

Response: Comment incorporated to clarify that the chapter is only required for aqueous, non-sterile products.

Comment Summary #2: Commenters suggested adding a statement to the exclude products with a Water Activity less than 0.75 from *Burkholderia cepacia* Complex (Bcc) <60> testing. Products, such as dry powders, would have no risk of Bcc contamination. Bcc contamination (and testing) should only be applicable to aqueous preparations for topical use.

Response: Comment incorporated for the reasons stated by the commenter.

Comment Summary #3: A commenter pointed out that the probe tack test as part of batch release testing does not add value for Transdermal Delivery Systems (TDS). The widely used peel-adhesion assays are more directly relevant to the user experience, and therefore a better control measure for batch release testing to ensure consistent product for the end user.

Response: Comment not incorporated. Probe tack is a critical quality attribute for TDS as recommended in the 2019 FDA guidance for TDS.

Comment Summary #4: A commenter suggested removing the section *Penetration Enhancer Content* to minimize the burden to the manufacturers.

Response: Comment not incorporated. The text specifies that only if a component of the formulation is claimed to be a penetration enhancer, it must be quantified and monitored. This section may be revised in the future to clarify the definition of penetration enhancer and how it should be evaluated.

Comment Summary #5: Under *Uniformity in Containers* test, in the text "(e.g., if the product assay range is 90.0%-120%, the range will be 85.0%-125.0%)," the commenter pointed out that it should be written "120.0%" instead of "120%."

Response: Comment incorporated. Decimal place was added to clarify the intended specificity.

Comment Summary #6: A commenter suggested that mechanical method terminology and definitions of failure modes specific to Peel Adhesion, Release liner, Tack, and Shear be further referenced or incorporated into the *USP*. To ensure conformity and consistency the commenter requested the addition of an informational general chapter for mechanical testing in alignment with the American Society for Testing and Materials (ASTM) International standards, ASTM D907 *Standard Terminology of Adhesives* and E6 *Standard Terminology Relating to Methods of Mechanical Testing*.

Response: Comment not incorporated. The comment is outside of the scope of General Chapter <3>.

Comment Summary #7: Under *Specific Tests for TDS, Peel Adhesion Test*, the commenter recommended a correction to the failure mode of the *Peel Adhesion Test* section. Specifically, the expected failure mode for peel adhesion is adhesive failure. The current explanation in the general chapter is correct, but the term cohesive failure in the parenthetical reference is incorrect.

Response: Comment incorporated for the reason stated by the commenter.

Comment Summary #8: Under *Specific Tests for TDS, Release Liner Peel Test*, the commenter suggested the following minor clarification to the Release Liner Peel Test paragraph to provide both mm/min rate and in/min rate.

Response: Comment incorporated.

Comment Summary #9: Under *Specific Tests for TDS, Tack Test*, the commenter suggested the following language be added to tack test: Adhesive failure should occur for each product tested. The overall mean of the maximum (tack) force results, using a minimum of 5 independent samples, must be within the acceptance range determined during product development.

Response: Comment not incorporated. The definition is too specific for the intended use of the chapter.

Comment Summary #10: Under *Specific Tests for TDS, Shear Test*, the text states "The shear test measures the cohesive strength of a TDS. It can be measured under static (see Static Shear Test) or dynamic conditions." The commenter requested a section for Dynamic Shear Test to be incorporated into this general chapter with the appropriate test description.

Response: Comment not incorporated because the proposed text allows for flexibility to use other approaches if needed. This comment may be addressed in a future revision of the chapter.

Comment Summary #11: Under *Specific Tests for TDS, Static Shear Test*, the commenter suggested the addition of adhesive failure and adhesive transfer with their respective definitions for shear testing.

Response: Comment not incorporated. The text of the general chapter contains enough information for its intended use.

Comment Summary #12: Under *Specific Tests for TDS, Static Shear Test*, the commenter suggested that the geometric mean calculation be referenced or incorporated into the text.

Response: Comment not incorporated. The text of the general chapter contains enough information for its intended use.

Comment Summary #13: In the *Introduction*, in the sentence: “The product quality attributes include the following: description, identification, assay (strength), impurities, **physicochemical properties**, uniformity of dosage units, water content, pH, apparent viscosity, **microbial limits**....”. the commenter suggested revising the sentence as follows: “The product quality attributes include the following: description, identification, assay (strength), impurities, physicochemical **and structural** properties, uniformity of dosage units, water content, pH, apparent viscosity, **microbial quality**....”

Response: Comment incorporated to provide clarity.

Comment Summary #14: In the *Particle Size* section, the commenter suggested adding that in general, a multi-tier specification is recommended.

Response: Comment not incorporated as it is more specific than necessary for the chapter’s intended use. The user can go to this level of detail if needed.

Comment Summary #15: In the *Emulsion Globule Size* section, the commenter suggested revising the text as follows: “*Therefore, control of the emulsion droplet and/or globule size should be considered a specific test for such products to ensure **batch-to-batch consistency**, homogeneity, physical stability, and **the absence of phase separation of in the drug product throughout the shelf life. In general, a multi-tier specification is recommended.***”

Response: Comment partially incorporated. The multi-tier specification was not incorporated, as it is more specific than necessary for the intended use of the chapter. The user can go to this level of detail if needed.

Comment Summary #16: Under *Uniformity in Containers, Products Packaged in Containers Other Than Tubes, Figure 1*, the commenter suggested to illustrate the sampling procedure in a clearer way.

Response: Comment not incorporated as the comment does not provide recommended changes. USP will consider a future revision based on submission of further information.

Comment Summary #17: In the *Particle Size* section, the “drug polymorphic form” is a part of particle size testing. However, based on significance of polymorphic stability testing for semi-solid dosage forms with suspended API, the commenter recommended including a separate test for polymorphic stability and including relevant information in the chapter.

Response: Comment not incorporated. This comment may be addressed in a future revision of the chapter.

Comment Summary #18: In the *Penetration Enhancer Content* section, the commenter revising the sentence as follows: “*If an excipient is **determined to be a penetration modifier**, a **qualitative test for identity and a quantitative test with acceptance limits for its content should be established.***”

Response: Comment not incorporated. This comment may be addressed in a future revision of the chapter.

Comment Summary #19: In the *Crystal Formation* section, the commenter suggested adding the following text: "If the finished product is designed to contain a suspended active drug substance, the properties of the suspension should be monitored over the product's shelf life."

Response: Comment not incorporated. This comment may be addressed in a future revision of the chapter.

Comment Summary #20: In the *In Vitro Drug Release Test*, the commenter suggested revising the sentence as follows: "For semisolid dosage forms, an in vitro release test (IVRT) is currently not mandatory for batch release; however, see *Semisolid Drug Products—Performance Tests* (1724) for appropriate contexts of use for an IVRT, as well as discussions on method development, experimental design, data analysis, suitable equipment, and their qualification, as well as other practical information."

Response: Comment incorporated to add clarity to the text.

Comment Summary #21: In the *Apparent Viscosity* section, the commenter recommended revising the sentence as follows: "*These techniques may be useful for product development using the principles of quality by design or for comparative physicochemical and structural characterization of the test and reference products to support a demonstration of bioequivalence in an abbreviated new drug application.*"

Response: Comment incorporated to add more clarity to the text.

Comment Summary #22: In the *Peel Adhesion Test*, the commenter pointed out that in vitro peel adhesion typically does not correlate to in vivo peel adhesion and suggested revising this section to clarify that no correlation exists.

Response: Comment not incorporated. The change is not necessary as the text does not refer to in vitro/in vivo correlation.

Comment Summary #23: Under Specific Test for TDS, the commenter suggested updating the text to state that the acceptance criteria for any tests related to TDS should be defined by in vitro testing results of representative batches, including clinical batches for which satisfactory in vivo adhesion performance has been demonstrated.

Response: Comment not incorporated. The text already contains this information.

Comment Summary #24: Under *Specific Tests for TDS*, the commenter suggested clarifying how data is generated and evaluated and adding a clarification on the meaning of "representative" batches used to set acceptance criteria.

Response: Comment not incorporated. The current text in the chapter is sufficiently clear.

General Chapter/Section(s): <5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests

Expert Committee: General Chapters—Dosage Forms

No. of Commenters: 4

Comment Summary #1: The commenter suggested revising the following text in the *Introduction*, under "*Drug Product General Quality Tests and Performance Quality Tests*" "...such as aerodynamic particle size distribution and/or droplet size distribution."

As follows to include the word "particle"

"...aerodynamic particle size distribution and/or droplet/**particle size** distribution."

This is also what was proposed in (601) **Response:** Comment incorporated to provide additional clarity.

Comment Summary #2: The commenter suggested revising the *General Quality Tests for Inhalation Drug Products* test under *Inhalation Suspension* from:

“Primary Particle Size Distribution”

to

“Primary Particle Size Distribution (for suspension)”

This change will be consistent with language used in *General Quality Tests for Nasal Drug Products* under *Nasal Spray*.

Response: Comment not incorporated. Primary PSD attribute is listed under *Inhalation Suspension*. The information is already provided.

Comment Summary #3: The commenter requested changing the term “Microbial Quality” to “Microbial Limits” in the chapter because “Microbial Quality” is not a testing item. The commenter states that it is not in line with other USP General Chapters <60>, <61>, or <62> or the recent FDA document (“Pharmaceutical Microbiology Manual”, Aug 2020, <https://www.fda.gov/media/88801/download> used the term “Microbial Examination”). The commenter also suggested instead using the term “Microbial Limits” (unchanged), “Microbial Examination”, (used in the above referenced FDA Manual and USP General Chapters <60> and <62>) or “Microbial Enumeration Test” (in <61>).

Response: Comment not incorporated. The term “Microbial Limits” has been retired and is replaced with “Microbial Quality.” Microbial quality speaks to Microbiological Quality (the number and types of microorganisms). Microbial Limits is now a defunct term with the retirement of old <61> in 2009.

Comment Summary #4: The commenter suggested revising the following sentence in Section 4 DESCRIPTION OF PRODUCT QUALITY TESTS under the “Foreign Particulate Matter” sub header from,

*“Following a detailed toxicological assessment of the type, origin, amount, and size of any foreign particulates of 10–25 µm and greater than 25 µm size ranges, **including fine particulates** (e.g., less than 10 µm), appropriate specifications should be established throughout the expiration dating period to confirm overall quality.”*

To:

*“Following a detailed toxicological assessment of the type, origin, amount, and size of any foreign particulates of 10–25 µm, greater than 25 µm size ranges, **and fine particulates (e.g., 1-10 µm).**”*

since the word “including” would imply, incorrectly, that the particulates size of 10-25 µm and greater than 25 µm are also considered fine particles.

Response: Comment incorporated to add criteria for fine particulates.

Comment Summary #5: The commenter requested adding a reference to chapter <1601> s in the last sentence of *Drug Product General Quality Tests and Performance Quality Tests* in addition to the existing reference to Chapter <601>.

Response: Comment incorporated. Reference to <1601> added for additional information.

Comment Summary #6: The commenter proposed changing the following text in the section on *Impurities and Degradation Products* from:

“...the acceptance criteria are set for individual, unspecified and total impurities and degradation products”

to

“...the acceptance criteria are set for specified, unspecified and total impurities and degradation products”

As it is better aligned with the current terminology used in ICH Q3B guideline.

Response: Comment incorporated by revising text as proposed to align with terminology that is currently in use.

Comment Summary #7: The commenter indicated that in *Table 1*, sterile products are listed but not non-sterile, and requested adding product expectations of sterile vs non-sterile.

Response: Comment not incorporated. Normally, a product is not defined by what it is not, but rather by the attribute that is critical.

Comment Summary #8: The commenter requested aligning micro control in USP chapters <5>, <60>, and <1111> for aqueous nasal and inhaled products. Aqueous nasal and inhaled products have a USP <61> MET spec and absence of specified testing USP <62> per USP <1111>. In addition, the absence of Bcc complex per USP <60>. <5> for aqueous inhaled products calls for sterility testing.

Response: Comment not incorporated. Chapters <61>, <62>, and <1111> do not cover sterility of nasal products and therefore do not apply. Microbiological aspects of non- aqueous inhaled drug products are addressed under "Microbial Quality," which also includes several USP references. Aqueous based inhalation, drug products (as stated above) should be sterile.

General Chapter/Section(s): <313> Molecular Weight and Polymer Chain Length Determination for Polypropylene Glycol Fatty Ethers/ Multiple Sections

Expert Committee(s): Excipients Test Methods

No. of Commenters: 1

Comment Summary #1: The commenter recommended changing the text “The following procedures are used to” to “The following gel permeation chromatography (GPC)/size exclusion chromatography (SEC) and nuclear magnetic resonance (NMR) procedures are used to” in the *Introduction* section.

Response: Comment incorporated. The Expert Committee agreed that this change offers more clarity to users.

Comment Summary #2: The commenter recommended changing the text “Compute the data using the same GPC/SEC software” to “Compute the peak area data using the same GPC/SEC software” in the *Analysis* section of *Method 1*.

Response: Comment not incorporated. There are no peak area data involved in the computing process. Peak retention times instead of peak areas are used as part of the raw data in the calculation. The computing process is based on the same principle with multiple data types involved, and therefore specific data types are not included.

Comment Summary #3: The commenter recommended changing the term of polydispersity to polydispersity index (PDI) in the *Analysis* section of *Method 1*.

Response: Comment not incorporated. Polydispersity is the term consistently used in the *USP-NF*.

Comment Summary #4: The commenter recommended changing the text “Integrate the areas” to “Integrate the peak areas” in the *Analysis* section of *Method 2*.

Response: Comment incorporated.

General Chapter <1083> Supplier Qualification
Expert Committee: General Chapters—Packaging and Distribution
No. of Commenters: 11

General

Comment Summary #1: The commenter recommended that the word “should” should be changed to “may.”

Response: Comment not incorporated. The words “should” and “may” have been used interchangeably in the chapter.

Comment Summary #2: The commenter recommended the chapter discuss supplier qualification elements related to clinical trial materials and machinability testing.

Response: Comment not incorporated. These two topics are outside the scope of the current chapter. The EC may consider this recommendation in the future.

Comment Summary #3: The commenter recommended the creation of a new USP General Chapter that is focused on how purchasers of finished dosage forms (e.g., health systems, wholesalers, distributors, compounders, clinics, retail pharmacies, and other settings) can apply a similar process to determine which suppliers they should buy from.

Response: Comment not incorporated. The comment is out of the scope of the proposal. The EC may consider this recommendation in the future.

Comment Summary #4: The commenter recommended discussing the proactive exchanges between suppliers and pharmaceutical manufacturers for supplier performance.

Response: Comment not incorporated. The chapter is intended to be a broad overview.

Comment Summary #5: The commenter recommended discussing the development of information technology allowing test data to be exchanged from suppliers to aid in decision making by pharmaceutical manufacturers.

Response: Comment not incorporated. The chapter is intended to be a broad overview.

Comment Summary #6: The commenter recommended clarifying the scope to establish guardrails as to when this chapter will be applied.

Response: Comment not incorporated. The applicability of informational general chapters are discussed in the General Notices.

Comment Summary #7: The commenter recommended editing the chapter to make it less prescriptive.

Response: Comment not incorporated. The chapter is a general informational chapter containing recommendations.

Comment Summary #8: The commenter suggests that the chapter is not necessary because other guidelines already exist.

Response: Comment not incorporated. Chapter was requested by stakeholders.

Comment Summary #9: The commenter suggested clearing up any confusion there may be between supplier qualification and good supply practices and supplier management lifecycle.

Response: Comment incorporated. The focus of the chapter is supplier qualification and does not broach the topics of good supply practices and supplier management lifecycle which are out of scope.

Comment Summary #10: The commenter suggested the chapter is too broad.

Response: Comment not incorporated. The chapter is designed to be broad.

Comment Summary #11: The commenter recommended the chapter be reviewed to ensure “suppliers” are described consistently.

Response: Comment incorporated. “Suppliers” are described consistently.

1.0 Introduction

Comment Summary #1: The commenter recommended the chapter should extend to contract service providers.

Response: Comment not incorporated. This material is already stated in the chapter.

Comment Summary #2: The commenter noted that outside of the US, chapters like this are used more stringently than in the US and regulators hold content within such chapters in a stricter sense than the USP outlines per the General Notices. As such, they requested that the word “guidelines” appear in the introduction.

Response: Comment not incorporated. Above 1000 General Chapters are informational and this is explained clearly in General Notices.

Comment Summary #3: The commenter recommended including a discussion on product integrity/condition upon arrival.

Response: Comment not incorporated. The best practice is to reject goods if they do not arrive in a usable condition. The current chapter is focused on supplier qualification. For more information on storage and distribution risks, see <1079> .

2.0 Scope

Comment Summary #1: The commenter recommends reviewing the chapter and eliminating elements that do not apply to the process of supplier qualification

Response: Comment incorporated. Chapter was reviewed and in instances where an element/topic was not related to the supplier qualification the corresponding text was deleted.

Comment Summary #2: The commenter suggests clarifying what is meant by “software”.

Response: Comment incorporated. A footnote was added to the chapter to define software

2.0 Scope (Figure 1)

Comment Summary #1: The commenter recommends clarifying what is meant by primary packaging.

Response: Comment incorporated. Examples of primary packaging are listed below the heading.

Comment Summary #2: The commenter suggests mentioning process aids, equipment, production consumables, and protective equipment.

Response: Comment not incorporated. Not all purchases should trigger a supply qualification process.

Comment Summary #3: The commenter recommended removing the example list under primary and secondary packaging.

Response: Comment not incorporated. There is value in giving examples of both primary and secondary packaging, so the lists are being maintained

3.0 Supplier Qualification Life Cycle (Table 1)

Comment Summary #1: The commenter recommended setting a timeline for the qualification process.

Response: Comment not incorporated. No current data exists to establish such a timeframe.

Comment Summary #2: The commenter stated that databases are updated and that the word “build” should not be used.

Response: Comment not incorporated. When the organizations are new, they will need to build a database.

Comment Summary #3: The commenter suggested organizations are not responsible for establishing the feasibility of a supplier to meet expectations.

Response: Comment not incorporated. The organization should assess, based on facts, that a supplier can meet the requirements to ensure product quality.

Comment Summary #4: The commenter recommended changes in the approved supplier qualification database be controlled by the change management process.

Response: Comment not incorporated. This is a GMP activity and changes should be made.

Comment Summary #5: The commenter recommends discussing the use of remote auditing.

Response: Comment incorporated. The chapter was revised to state that remote or virtual audits can be taken into consideration during supplier assessment.

Comment Summary #6: The commenter suggested the inclusion that establishing and sharing key performance indicators are necessary.

Response: Comment incorporated. The chapter was revised to state that one should establish and share key performance indicators.

Comment Summary #7: The commenter suggested adding text regarding requalification.

Response: Comment not incorporated. Concepts discussed in this chapter can be applicable to the requalification process.

3.1 Preparation

Comment Summary #1: The commenter recommended finance and legal be removed from this section.

Response: Comment incorporated. Sections removed because they are not necessary for the preparation step of supplier qualification.

3.2 Identification and Selection of Supplier for Materials and Services

Comment Summary #1: The commenter suggested that these requirements should be based on criticality/risk evaluation and not be mandatory for all materials/services.

Response: Comment incorporated. The chapter states that risk (risk assessment) should be considered when selecting a supplier of a material or service.

Comment Summary #2: The commenter suggested that, if needed, confidentiality and nondisclosure agreements should be signed and exchanged with suppliers.

Response: Comment incorporated. The chapter states that, when necessary, confidentiality agreements should be executed and exchanged.

Table 2

Comment Summary #3: The commenter suggested that the assessment of all the risks is not relevant for low criticality material or for well-known suppliers.

Response: Comment incorporated. The table was revised to allow consideration of material and supplier risk.

Comment Summary #4: The commenter suggested that the section on supplier selection should be removed because it is already covered in another USP chapter.

Response: Comment not incorporated. This topic is not available in other USP Chapters.

3.3 Evaluation and Acceptance

Comment Summary #1: The commenter recommended using the term “supplier termination” vs. “supplier disqualification”.

Response: Comment not incorporated. Disqualification and termination are not synonymous. Disqualification is the process of determining that a material or service is no longer required and then executing the termination process.

Comment Summary #2: The commenter recommended clarifying that the tolerance is related to the goods or service and not the supplier.

Response: Comment incorporated to clarify this point.

Comment Summary #3: The commenter suggested stating that contracts and quality agreements are not required for all suppliers and should be reflected in the text.

Response: Comment incorporated to clarify that contracts and agreements are not required for all suppliers.

Comment Summary #4: The commenter suggests financial requirements should be separate from GMP requirements.

Response: Comment not incorporated. There is no mention of financial requirements in section 3.3.

3.3. Evaluation and Acceptance (Onsite Audits)

Comment Summary #5: The commenter suggested stating that all elements are not required for all contracts or quality agreements.

Response: Comment incorporated. The chapter states that the various elements should, not must, be included.

Comment Summary #6: The commenter recommended mentioning remote audit as a possibility if site audit is not possible based on criticality/risk evaluation.

Response: Comment incorporated. The comment was incorporated to clarify that remote audits may be considered in certain situations.

3.3. Evaluation and Acceptance (Sample Request)

Comment Summary #7: The commenter recommended adding a comment that the number of samples should be based on criticality/risk evaluation and not state a specific minimums requirement (three batches).

Response: Comment not incorporated. The minimum sample number is consistent with [FDA requirements](#).

3.4 Performance monitoring

Comment Summary #1: The commenter suggested that supplier's performance should be appropriately checked, and the result recorded at receipt of deliveries.

Response: Comment incorporated to add these recommendations

Comment Summary #2: The commenter suggested that an external standard be required when determining performance monitoring.

Response: Comment not incorporated. It is not always necessary to use a standard in determining performance.

Comment Summary #3: The commenter suggests that certificates and authorizations may only need re-evaluation at regular intervals for certain supplier types.

Response: Comment not incorporated. Greater discussion is needed around what is meant by "certain supplier type."

Comment Summary #4: The commenter recommended adding more detail to the section.

Response: Comment not incorporated. The commenter was not specific regarding what detail should be added to the section.

Comment Summary #5: The commenter recommended the chapter have a proactive approach when discussing performance monitoring.

Response: Comment incorporated. As written, the chapter discusses proactive measures that should be in place to ensure adequate monitoring of supplier performance.

Evaluation of Supplier Performance

Comment Summary #6: The commenter suggested that if a quality risk-based approach is used, the frequency of the evaluation should be based on supplier / material risk.

Response: Comment incorporated. Revised to state that the frequency of evaluation should be based on criticality.

Comment Summary #7: The commenter suggested that if needed, the quality agreement should be reviewed and updated.

Response: Comment incorporated. Revised to state quality agreement should be reviewed and updated, as necessary.

Comment Summary #8: The commenter suggested that financial requirements should be separate from GMP requirements.

Response: Comment incorporated. Revised to remove any mention of financial requirements.

3.5 Supplier disqualification

Comment Summary #1: The commenter suggested that change control should also be applied in the qualification process.

Response: Comment not incorporated. When talking about a product, change control is already implied.

Comment Summary #2: The commenter suggested that the disqualification process should be documented in a system but not automatically through a change control program.

Response: Comment not incorporated. Even if the supplier is no longer approved, you still need to document, and this goes through change control.

Comment Summary #3: The commenter suggested that completion of tasks and the process of retrieving outstanding samples are managed together.

Response: Comment incorporated. Revised to include a bullet that states that a process should be established to retrieve work and samples.

General Chapter/Section(s): <1212> Probe Tack Test/ Multiple Sections

Expert Committee(s): General Chapters – Dosage Forms

No. of Commenters: 2

Comment Summary #1: The commenter requested that the definitions and interpretations in the general chapter <1212> Probe Tack Test be in alignment with the American Society for Testing and Materials (ASTM) International standards, ASTM D907 *Standard Terminology of Adhesives* and ASTM E6 *Standard Terminology Relating to Methods of Mechanical Testing*.

Response: Comment incorporated. The reference to the ASTM was added to the text.

Comment Summary #2: The commenter requested the following language be added to the end of the paragraph in the introduction to clarify the failure mode for probe tack testing: Each test should result in clean removal of the probe with all adhesives remaining on the TDS (i.e., an indication of adhesive failure mode).

Response: Comment incorporated for clarity.

Comment Summary #3: The commenter suggested a slight modification to the apparatus section to clarify probe tack testers with different configurations and fixtures. The language in the general chapter describing the two types of instruments and fixtures could be improved upon to provide clear and concise descriptions of the fixtures.

Response: Comment not incorporated. The description offers enough flexibility to the users in selecting the appropriate equipment.

Comment Summary #4: The commenter proposed a slight modification to the apparatus section to clarify probe tack testers with different configurations and fixtures. The language in the general chapter describing the two types of instruments and fixtures could be improved upon to provide clear and concise descriptions of the fixtures.

Response: Comment incorporated.

Comment Summary #5: In *Figure 1. Schematic example of a probe tack testing apparatus*, the comment suggested that the image be updated to clearly identify the adhesive and backing of the transdermal like the image from ASTM 02979-16.

Response: Comment incorporated to clearly identify the adhesive and backing of the transdermal like the image from ASTM 02979-16.

Comment Summary #6: In the *Procedure* section, the comment recommended that the content within this section could be improved upon to provide a clear and concise description of tack testing. The commenter suggested adding additional information in the

steps describing the set-up, sample preparation, testing and results be split into sub-sections, as well as to separate the sample preparation by the apparatus and fixture.

Response: Comment not incorporated. The current text provides enough information to the users to provide a framework for procedures.

Comment Summary #7: In the *Procedure* section, under *Reporting*, the commenter stated that the language about how to report probe tack was removed, and the reporting language in General Chapter <3> was clarified. The commenter suggested that the reporting language be added back to General Chapter <1212> in alignment with the proposed language for General Chapter <3>.

Response: Comment not incorporated. The text of the chapter provides enough general guidance to the users in combination with the text of General Chapter <3> *Topical and Transdermal Drug Products – Quality Tests*, which was revised.

Comment Summary #8: In the *Introduction* section, the commenter proposed changing the text to “*This test method involves bringing the tip of a clean probe of defined material and diameter into contact with the adhesive surface...*”

Response: Comment not incorporated. The text defining the probe is already in the text.

Comment Summary #9: In the *Apparatus* section, the second paragraph assumes that the adhesive surface is always fixed but there are instruments which utilize a fixed probe (i.e., the adhesive surface is moved to make contact with the probe). Both movements should be described in the text. Additionally, the term “test system” is sometimes used to define a TDS sample; it may be more accurate to use the term “apparatus” or “instrument” in this statement.

Response: Comment partially incorporated.

Comment Summary #10: the commenter suggested updating Figure 1 to clearly display all portions of the apparatus.

Response: Comment partially incorporated. The figure was modified to indicate how the sample is inserted into the equipment.

Comment Summary #11: In *Figure 2* the commenter suggested revising the figure description as follows: “*Figure 2. Alternate fixture: Upside-down view of rigid plate with predrilled holes.*”

Response: Comment incorporated for clarity.

Comment Summary #12: In the *Procedure* section, the commenter recommended including text to indicate that the method should be performed under specified conditions, such as including the following at the beginning of the section: “***Prior to performing the measurement, the test sample is conditioned at the specified testing conditions (temperature, humidity) for a minimum specified duration.***”

Response: Comment incorporated to provide additional information about specified conditions under which the method should be performed.

Comment Summary #13: Under *Procedure*, the commenter noted that there may be adhesive residue on the probe end that the user cannot see; therefore, the probe end should be cleaned between measurements according to a cleaning protocol providing for the use of specific solvents to ensure the removal of all adhesive debris from the probe surface after each measurement.

Response: Comment not incorporated. Cleaning between measurements is not always necessary.

Comment Summary #14: The commenter suggested some minor edits:

“Remove the probe **and from the** adhesive surface at a constant reversing speed, e.g., 10 mm/s.”

“Record ~~the~~ tack as the maximum force required to break the bond.”

“~~The tack~~ Tack is expressed by recording the maximum force to break the bond between the probe and the adhesive surface or the area under the force per time to break that bond.”

Response: Comment incorporated for clarity.

Monographs

Monograph/Section(s): Amlodipine Besylate / Multiple Sections

Expert Committee: Small Molecules 2

No. of Commenters: 2

Comment Summary #1: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Comment Summary #2: The commenter recommended loosening the system suitability requirement for the *Tailing factor* from NMT 2.0 to NMT 2.5 in the *Assay* and the *Organic Impurities* test based on the supporting data

Response: Comment incorporated.

EC-initiated Change: The Expert Committee determined to replace the impurity name USP Amlodipine Related Compound E RS in *Table 2* of the test for *Organic Impurities* with “Amlodipine ethyl analog” as no USP Reference Standard is available with this name.

Monograph/Section(s): *Bifobacterium longum* subsp. *longum* / Additional requirements, Packaging and Storage

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 0

EC-initiated Change: Under *Additional Requirements, Packaging and Storage*, the text was changed to indicate “Protect from moisture using high barrier foil laminate bags and store at or below 4°”, instead of “Preserve in high barrier foil laminate bags and store at or below 4°”.

Monograph/Section(s): *Bifobacterium bifidum* / Additional requirements, Packaging and Storage

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 0

EC-initiated Change: Under *Additional requirements, Packaging and Storage*, the text was changed to indicate “Protect from moisture using high barrier foil laminate bags and store at or below 4°”, instead of “Preserve in high barrier foil laminate bags and store at or below 4°”.

Monograph/Section(s): Black Cumin Seed Thymoquinone Oil / Definition, Identification, Composition, and Specific Tests

Expert Committee: Botanical Dietary Supplements

No. of Commenters: 2

Comment Summary #1. Under the *Definition*, the commenter questioned the feasibility to always maintain 3.0% thymoquinone in oils from various regions like the Middle East, USA, and the Indian subcontinent.

Response: Comment not incorporated. A different monograph for the regular oil, Black Cumin Seed Oil (NLT 0.5% and NMT 2.9% % of thymoquinone), may be also developed.

Comment Summary #2. Under *Specific tests, Acid value*, it was indicated that deviations of acid value in Black Cumin seed oil with 3% thymoquinone are high to state the maximal acid value of 2.5. It's suggested to be NMT 4.0.

Response: Comment not incorporated. The acid value of NLT 2.5 is aligned with other *USP* monographs for vegetable oils.

EC-initiated Change #1: Under *Identification B. HPTLC for Articles of Botanical Origin <203>*, the EC removed the description of the band due to carvacrol from the *Standard Solution B* and the *Sample solution* as this compound was not properly detected.

EC-initiated Change #2: Under *Composition, Content of Monoterpenes*, the EC included the *USP Black Cumin Seed Oil RS as Standard Solution B for Chromatographic similarity* in the *Suitability Requirements* section.

Monograph/Sections: Calcium Ascorbate / Multiple Sections

Expert Committee: Non-Botanical Dietary Supplements

No. of Commenters: 0

EC-Initiated Change #1: Retain the original definition i.e., “Calcium Ascorbate contains NLT 98.0% and NMT 101.0% of calcium ascorbate dihydrate ($C_{12}H_{14}CaO_{12} \cdot 2H_2O$), calculated on the as-is basis.”

EC-Initiated Change #2: In the Assay section, remove the “Content of Ascorbate” title and revise the formula to calculate Calcium Ascorbate

EC-Initiated Change #3: In the Assay section, move the *Content of Calcium* test to the *Other Components* section

EC-Initiated Change #4: In the Assay section, delete the Content of Calcium Ascorbate test

Monograph/Section(s): Cevimeline Hydrochloride / Multiple Sections

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment Summary #1: The commenter requested to update the specification from NLT 98.0% and NMT 102.0% of cevimeline hydrochloride ($C_{10}H_{17}NOS \cdot HCl \cdot \frac{1}{2}H_2O$) to NLT 98.0% and NMT 102.0% of cevimeline hydrochloride ($C_{10}H_{17}NOS \cdot HCl$) in the *Definition*, to be consistent with the *Assay*.

Response: Comment incorporated.

Comment Summary #2: The commenter indicated that the limit for Cevimeline *trans*-isomer in the test for *Organic Impurities* is different from what has been approved.

Response: Comment incorporated. The *Acceptance criteria* for Cevimeline *trans*-isomer has been widened from NMT 0.30% to NMT 0.50% to be consistent with the FDA-approved specification.

Comment Summary #3: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Comment Summary #4: The commenter indicated that the *Acceptance criteria* for *Water Determination* is different from what has been approved by the agency.

Response: Comment incorporated. The *Acceptance criteria* for Water Determination has been updated from 3.2-4.2 to 3.2-4.50 to be consistent with the FDA-approved specification.

Comment Summary #5: The commenter recommended including a test for determination of pH as the drug substance is a hydrochloride salt.

Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

EC-Initiated Change #1: The Expert Committee updated the structure in the chemical information section to be consistent with the drug product package insert.

Monograph/Sections: Choline Chloride / Multiple Sections
Expert Committee: Non-Botanical Dietary Supplements
No. of Commenters: 0

EC-initiated Change #1: Added an additional note to the *Related Compounds* procedure to help users distinguish, identify, and address artifact and impurity peaks in the HPLC-CAD chromatograms.

EC-initiated Change #2: Instructions for the *Standard response line* in the test procedure for the *Limit of Total Amines* contained an error in representation of the accurate cumulative concentrations after each addition of the *Standard solution*, which should be calculated by taking into account the accurate total volume of the solution in the vessel. Instructions to calculate the correct and accurate cumulative concentrations have been added to the text.

Monograph/Section(s): Clonidine Hydrochloride Tablets / Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section(s): Dobutamine Hydrochloride / Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section(s): Emulsifying Wax / Specific tests
Expert Committee(s): Complex Excipients
No. of Commenters: 2

Comment Summary #1: The commenters recommended clarifying the calculation of fatty acid methyl ester proportions. Currently, there are no specific details in how rT should be calculated, which is the sum of the peak areas of the fatty acid methyl esters in the chromatogram of the *Test solution*.

Response: Comment incorporated. In the text, rT has been defined as the peak areas of three fatty acid methyl esters i.e., Methyl Myristate, Methyl Palmitate, and Methyl Stearate.

Monograph/Section(s): Hydroxychloroquine Sulfate Compounded Oral Suspension
Expert Committee: Compounding
Number of Commenters: 1

Comment Summary #1: The commenter indicated that the formulation allows for the use of tablets or powder and requests dividing the formulations into two formulae to avoid confusion (e.g., bulk powder or tablets ground to powder).

Response: Comment not incorporated. The proposed change is not consistent with the USP Style Guide.

Comment Summary #2: The commenter indicated that the second formula uses Crème de Menthe as a flavoring agent and requests noting that this component contains alcohol.

Response: Comment not incorporated. The alcohol content within 0.2 mL of Crème de Menthe flavoring is not a material quantity.

Comment Summary #3: The commenter indicates the <51> statement follows the second formulation and is unsure if it also applies to the first.

Response: Comment not incorporated. Antimicrobial Effectiveness Testing <51> is currently being performed for first formulation.

Comment Summary #4: The commenter indicated that the monograph uses proprietary ingredients as excipients where there is no information about the identity of the excipient provided in the monograph.

Response: Comment not incorporated. USP does not provide information on commercially available excipients because this is proprietary information. Information on the content of excipients is readily available from suppliers.

Comment Summary #5: The commenter indicates this monograph is missing the *Appearance* section.

Response: Comment incorporated. The *Appearance* section has been added.

Comment Summary #6: The commenter indicated that the monograph has a general pH provided that does not correlate with the pHs specified for each formulation.

Response: Comment incorporated. General pH information included before the revision has been removed.

Comment Summary #7: The commenter requested the type of container closure system specify material (e.g., metal or plastic).

Response: Comment partially incorporated. Container material composition has been incorporated according to <795>.

Monograph/Section(s): Ipratropium Bromide / Organic Impurities
Expert Committee: Small Molecules 5
No. of Commenters: 2

Comment summary #1: The commenter recommended including a suitable limit for the anhydrous form in the *Water Determination* test, as the monograph is applicable to both the monohydrate and the anhydrous forms of Ipratropium Bromide

Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

Comment summary #2: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Comment summary #3: The commenter indicated replacing a TLC procedure with more accurate LC-MS procedure will require contract analysis for release and testing of their product as availability of LC-MS equipment is limited in their facility.

Response: Comment not incorporated. The Expert Committee determined that the proposed LC-MS method is more accurate and suitable for its intended use.

Monograph/Section(s): Mesalamine Extended-Release Capsules / Organic Impurities
Expert Committee: Small Molecules 2
No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section(s): Methylene Blue / Multiple Sections
Expert Committee: Small Molecules 2
No. of Commenters: 2

Comment Summary #1: The commenter recommended removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement on the topic.

Comment Summary #2: The commenter requested retaining the tests for *Arsenic*, and *Copper or Zinc* elemental impurities; and suggested adding tests for ten other elemental impurities to be consistent with the corresponding European Pharmacopeia monograph.

Response: Comment not incorporated. The USP Expert Committee decided that the tests for elemental impurities should not be in drug substance monographs. This decision is consistent with previous monographs and in alignment with the general strategy for controlling elemental impurities in drug products.

Comment Summary #3: The commenter requested widening the limits for *Loss on Drying* (LOD) to “8.0 – 24.0%” to accommodate the pentahydrate form.

Response: Comment not incorporated. The LOD test is outside the scope of the current revision proposal. Additionally, the *Acceptance criteria* for LOD (8.0 – 22.0%) are consistent with approved specifications.

Monograph/Section(s): Micafungin Sodium / Multiple Sections
Expert Committee: Small Molecules 1
No. of Commenters: 7

Comment Summary #1: The commenter indicated that the *Acceptance criteria* for the *pH* test is different from that in the approved products.

Response: Comment incorporated. The *Acceptance criteria* for the *pH* test was revised from “5.8-7.2” to “5.0-7.2” to accommodate other FDA-approved products.

Comment Summary #2: The commenter indicated that the *Acceptance criteria* for the *Water Determination* test is different from that in the approved products

Response: Comment incorporated. The *Acceptance criteria* for the *Water Determination* test was revised from “NMT 2.5%” to “NMT 8.0%” to accommodate other FDA-approved products.

Comment Summary #3: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement.

Comment Summary #4: The commenter requested adding *Organic Impurities, Procedure 2* for the commenter's approved analytical procedure and acceptance criteria.

Response: Comment not incorporated. The Expert Committee determined that the proposed *Organic Impurities* test is suitable as a public standard.

Comment Summary #5: The commenter requested revising the *Acceptance criteria* for the *Water Determination* test to NMT 5.0% based on their approved application.

Response: Comment incorporated. The *Acceptance criteria* for the *Water Determination* test was revised from "NMT 2.5%" to "NMT 8.0%" to accommodate other FDA-approved products.

Comment Summary #6: The commenter requested revising the *Acceptance criteria* for the *pH* test range to "5.0-7.0" based on their approved application.

Response: Comment incorporated. The *Acceptance criteria* for the *pH* test was revised from "NMT 2.5%" to "NMT 8.0%" to accommodate other FDA-approved products.

Comment Summary #7: The commenter requested revising the acceptance criterion for the *Residue on Ignition* test based on their approved application.

Response: Comment incorporated. The acceptance criterion for the *Residue on Ignition* test was widened from "5.2%-5.8%" to "4.8%-5.8%".

Comment Summary #8: The commenter requested changing the molecular weight of micafungin sodium from 1292.26 to 1292.77, removal of the free acid information under the chemical information section, and clarification of some impurity names in the *Organic Impurities* test.

Response: Comment partially incorporated. The chemical information for the free acid of micafungin sodium-micafungin is not needed and was removed. Regarding molecular weight and chemical names, USP follows current IUPAC recommendations.

Comment Summary #9: The commenter indicated that the proposed *Organic Impurities* procedure lacks selectivity and provided their method and validation for the Expert Committee's consideration.

Response: Comment not incorporated. Based on the supporting information, the Expert Committee determined that the proposed *Organic Impurities* procedure is suitable for the intended use.

Comment Summary #10: The commenter requested revising the *Acceptance criteria* for the *Water Determination* test to "NMT 7.5%" based on their approved application.

Response: Comment incorporated. See the Response in #2.

Comment Summary #11: The commenter requested revising the *Acceptance criteria* for the *Specific Rotation* test from "-20° to -22°" to "-20° to -27°" based on the test method in their approved application.

Response: Comment not incorporated. The proposed acceptance criteria can be met for the commenter's Micafungin Sodium by using the USP conditions.

Comment Summary #12: The commenter requested revising the *Acceptance criteria* for the *Water Determination* test to "NMT 8.0%" based on their approved application.

Response: Comment incorporated. See Response in #2.

Comment Summary #13: The commenter requested revising the *Acceptance criteria* for the *Specific rotation* test from "-20° to -22°" to "-20.0° to -25.0° on the anhydrous basis", based on the test method in their approved application.

Response: Comment not incorporated. The commenter's sample solvent, concentration, and temperature of analysis are not the same as USP's. The commenter did not provide additional data using the USP conditions.

Comment Summary #14: The commenter indicated that the proposed impurity profile and impurity limits are related to a specific manufacturing process and recommended removing the *Organic Impurities* test from the monograph.

Response: Comment not incorporated. The Expert Committee determined that the proposed *Organic Impurities* test is suitable as a public standard.

Comment Summary #15: The commenter requested changes to Multiple Sections in the monograph to accommodate the different hydration form of Micafungin Sodium.

Response: Comment not incorporated. The referenced hydrated form of micafungin sodium is not used in a currently FDA-approved drug product.

Comment Summary #16: The commenter indicated that issues with solution stability, and method sensitivity and interference were encountered during *Assay* and *Organic Impurities* method verifications. The commenter suggested an increase of injection volume.

Response: Comment not incorporated. The proposed *Assay* and *Organic Impurities* methods, supported by validation, are suitable for the intended use.

Comment Summary #17: The commenter requested revising the *Acceptance criteria* for the *Water Determination* test to “12.0%”, based on their information.

Response: Comment not incorporated. The referenced material is not used in a currently FDA-approved drug product.

EC-Initiated Change #1: The UNII code IS1UP79R56 has been added for Micafungin Sodium under the chemical information section.

EC-Initiated Change #2: To provide flexibility and avoid confusion to the users, the notes (*Note—Standard and sample weighings should be performed with the relative humidity below 10% because of the hygroscopicity*) in the *Assay* and *Organic Impurities* tests were removed.

EC-Initiated Change #3: The composition of the USP Micafungin Sodium RS was removed from the *USP Reference Standards <11>* section to be in alignment with the current USP practice.

Monograph/Section(s): Micafungin for Injection / Multiple Sections

Expert Committee: Small Molecules 1

No. of Commenters: 3

Comment Summary #1: The commenter indicated that the *Acceptance criteria* in the *Definition* and *Assay* are different from those in the approved applications.

Response: Comment not incorporated. The *Acceptance criteria* in the *Definition* and *Assay* are consistent with the sponsor’s approved application. If necessary, the Expert Committee will consider future revisions to the monograph upon the receipt of new supporting data.

Comment Summary #2: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement.

Comment Summary #3: The commenter recommended removing the specified impurity Deoxy micafungin, controlled at NMT 0.5% from the list of impurities (*Table 1*) as it is sufficiently controlled in the drug substance.

Response: Comment not incorporated. The proposed Deoxy micafungin limit is approved by the FDA and is included in *Total impurities*.

Comment Summary #4: The commenter indicated that there could be difficulties with laboratories testing with UV-PDA due to the availability of the equipment and recommended including <197U> as an alternative method for *Identification A* test.

Response: Comment not incorporated. The identification test based on UV-PDA is more specific than the <197U> test and can be found in many USP drug product monographs.

Comment Summary #5: The commenter requested clarification of some impurity names in the *Organic Impurities* test.

Response: Comment not incorporated. USP follows current IUPAC recommendations.

Comment Summary #6: The commenter recommended including a specific drug product related acceptance criteria for the *Bacterial Endotoxins* test.

Response: Comment not incorporated. USP's approach to Bacterial Endotoxins is to direct each user to the General Chapter <85>, where the limits are calculated.

Comment Summary #7: The commenter indicated that the proposed impurity profile and impurity limits are related to a specific manufacturing process and recommended removing the *Organic Impurities* test from the monograph.

Response: Comment not incorporated. The *Organic Impurities* method and *Acceptance criteria* are based on FDA approval, not on a proprietary process.

EC-Initiated Change #1: To provide flexibility and avoid confusion to the users, the notes (*Note—Standard and sample weighings should be performed with the relative humidity below 10% because of the hygroscopicity*) in the *Assay* and *Organic Impurities* tests were removed.

EC-Initiated Change #2: The composition of the USP Micafungin Sodium RS was removed

Monograph/Section(s): Morphine Sulfate Compounded Oral Solution / Multiple Sections

Expert Committee(s): Compounding

Number of Commenters: 1

Comment Summary #1: The commenter indicated the Morphine Sulfate powder from Roxane Laboratories in Columbus, OH is no longer available.

Response: Comment not incorporated. Morphine sulfate products from Roxane are still available in the US.

Comment Summary #2 The commenter requested the monograph include a statement that the oral solution contains sodium benzoate as a preservative.

Response: Comment not incorporated. The product is diluted to a concentration that is likely not harmful.

Comment Summary #3: The commenter indicated that the monograph does not include a statement indicating that the monograph passed <51> testing.

Response: Comment not incorporated. Statement moved to BUD section that Monograph Development Subcommittee (MDSC) agreed upon in early 2022.

Comment Summary #4: The commenter requested the type of container closure system specify material (e.g., metal or plastic).

Response: Comment partially incorporated. Container material composition incorporated according to <795>.

Comment Summary #5: The commenter requested the monograph include the following for safety information, "This medication has a risk of addiction, abuse, and misuse; and life-threatening respiratory depression; accidental ingestion; neonatal opioid withdrawal syndrome; and risks from concomitant use with benzodiazepines or other central nervous system depressants."

Response: Comment not incorporated. Safety information is outside the purview of the MDSC.

Monograph/Section(s): Neomycin Sulfate / Multiple Sections

Expert Committee(s): Biologics Monographs 4

No. of Commenters: 1

Comment Summary #1: The commenter asked if it is possible to delete the *Identification A* test.

Response: Comment not incorporated. Two orthogonal methods for identification are preferred.

Comment Summary #2: The commenter asked if it is appropriate to prepare the USP Neomycin B RS solution and USP Neomycin A RS solutions separately and then make them together in the tests for *Organic Impurities* and *Composition of Neomycin Sulfate*.

Response: Comment not incorporated. No change is needed. The *Standard solution* is prepared appropriately to keep the final concentration the same as the monograph.

Comment Summary #3: The commenter asked what the limit of “carbonate-free” is in the post-column reagent preparation in the tests of *Organic Impurities* and *Composition of Neomycin Sulfate*.

Response: Comment incorporated. The sentence is changed to “Prepared from 50% sodium hydroxide TS in water, carbon dioxide-free”.

Comment Summary #4: The commenter stated that the sample concentration is too high in the tests for *Organic Impurities* and *Composition of Neomycin Sulfate*.

Response: Comment not incorporated. The peak shape of the neomycin B peak at this concentration does not affect the quantification of other peaks.

Comment Summary #5: The commenter stated that they had difficulty performing the water content for USP Neomycin B RS, which needs a water content test performed at the time of use.

Response: Comment incorporated. The certificate of USP Neomycin B RS is revised to include suggested solvent for the water content test.

Monograph/Sections: Oxymorphone Hydrochloride / Organic Impurities

Expert Committee: Small Molecules 2

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section(s): Polyethylene Glycol 30 Dipolyhydroxystearate 5 / Specific Tests

Expert Committee(s): Complex Excipients

No. of Commenters: 1

Comment Summary #1: The commenter highlighted that the current monograph proposal has a limit of NMT 10.0 for hydroxyl value whereas the limits for the corresponding *European Pharmacopeia* monograph are 12 to 30. The commenter suggested to use this limit in the current proposal to further align it with the *European Pharmacopeia* monograph.

Response: Comment not incorporated. It was highlighted by USP that the actual limit for hydroxyl value is 12 to 30 in the current monograph proposal and not NMT 10. An appropriate screenshot of the hydroxyl value test was also shared with the commenter.

Monograph/Section(s): Polyethylene Glycol 12 Cetostearyl Ether / Multiple Sections

Expert Committee(s): Complex Excipients

No. of Commenters: 5

Comment Summary #1: The commenter commented about a statement in the briefing, suggesting USP to point out that the ingredients are derived not only from coconut oil. The longer fatty acids are generally derived from palm kernel oil.

Response: Comment not incorporated. Material in the briefing is not used in the final text.

Comment Summary #2: The commenter suggested to add the word ‘Procedure’ as the heading for the Identification D test.

Response: Comment not incorporated. The word ‘Procedure’ was not included per current *USP* style.

Monograph/Section(s): Prasugrel Hydrochloride / Organic Impurities
Expert Committee: Small Molecules Monograph 2
No. of Commenters: 2

Comment Summary #1: The commenters indicated that the chemical information and re for “Prasugrel desacetoxy analog” did not agree with each other.

Response: Comment incorporated. The correct chemical name for “Prasugrel desacetoxy analog” was updated within *Table 2*.

Monograph/Section(s): Roflumilast / Multiple Sections
Expert Committee: Small Molecules 5
No. of Commenters: 4

Comment summary #1: The commenter commented that there is salt precipitation when *Solution B* is increased up to 70 percent in the *Assay* method.

Response: Comment not incorporated. The Expert Committee determined that the method is consistent with validation data and suitable for its intended use. USP lab evaluation of the method did not show back pressure or repeatability issue.

Comment summary #2: The commenter reported difficulty in getting suitable responses from the *Standard solution* and meeting the *Signal-to-noise ratio* requirement in the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee determined that the method is consistent with validation data and suitable for its intended use.

Comment summary #3: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Comment summary #4: The commenter requested including two specified impurities, Roflumilast N-oxide impurity and Di-cyclopropyl impurity, captured in their in-house specification with a limit of NMT 0.15% in the test for *Organic Impurities*.

Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

Comment summary #5: The commenter suggested that the sample weight of about 500 mg-5g as per the <921> is not sufficient and requires about 10g of the sample in the test for *Water Determination*.

Response: Comment not incorporated. The Expert Committee determined that the method is consistent with validation data and suitable for its intended use.

Monograph/Section(s): Sildenafil Injection / Multiple section
Expert Committee: Small Molecules 5
No. of Commenters: 1

Comment summary #1: The commenter recommended removing the “Limit of 5-Hydroxymethylfurfural” test under *Organic impurities* section, as this impurity is not a degradation product and indicated that the proposed limit may not be appropriate for a public standard.

Response: Comment incorporated. The identified test was removed.

Comment summary #2: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Monograph/Sections: Silver Nitrate / Assay

Expert Committee(s): Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter observed that the replaced titrimetric procedure in the Assay was not struck through for deletion in the proposal when published in *PF*.

Response: Comment incorporated. This was an error in the document code to not show the strikethrough. The error in the document appearance will not be corrected in the published *PF* proposal, but it will appear correct in the official texts in *USP-NF*.

Monograph/Section(s): Sodium Chloride Compounded Injection / Multiple Sections

Expert Committee: Compounding

Number of Commenters: 1

Comment Summary #1: The commenter indicated the monograph includes Sodium Chloride but does not specifically refer to it as the bulk powder

Response: Comment incorporated.

Comment Summary #2: The commenter requested the quantity of Sodium Chloride be changed from 7.02 g to 7020 mg because the final concentration is listed as 234 mg/mL to reduce the risk of medication error.

Response 2: Comment not incorporated. The Monograph Development Subcommittee (MDSC) states that listing a quantity of 7020 mg is more prone to medication errors than 7.02 g.

Comment Summary #3: The commenter indicated the BUD in the monograph is significantly longer than the limits stated in <797>.

Response: Comment not incorporated. Requirements in monographs supersede requirements in general chapters where they may differ.

Comment Summary #4: The commenter requested the osmolar concentration be added to the monograph.

Response: Comment incorporated. A statement was added to the labeling section to indicate the theoretical osmolar concentration.

Comment Summary #5: A commenter requested the monograph include the following from the FDA-approved product: "Preservative Free. Discard unused portion. Use only if solution is clear and seal intact."

Response: Comment not incorporated. The *Labeling* section of a monograph only includes warnings on the immediate label on the container.

Monograph/Section(s): Sodium Ascorbate / Multiple Sections

Expert Committee: Non-Botanical Dietary Supplements

Commenters: 1

Comment Summary #1: The commenter noted that the *Acceptance criteria* under the test for *Content of Sodium Ascorbate* are revised from "99.0%-101.0%" to "99.0%-102.5%" using the calculation formula of adding the individual percentages of Ascorbate and Sodium contents. The commenter raised the following concern "The proposed acceptance criteria for Ascorbate are 88.0% - 90.5% and those for Sodium are 11.1% - 12.1%. So, the theoretical acceptance

criteria for sum of Ascorbate and Sodium should be 99.1% - 102.6%, which are different from the proposed acceptance criteria” and recommended revising the acceptance criteria and the definition accordingly.

Response: Comment not incorporated. Expert Committee members recommended using the original calculation instead of the proposed revision published in *PF* for the content of Sodium Ascorbate i.e., calculate based on only content of Ascorbate and retain the original limits of 99.0% - 101.0%.

EC-Initiated change #1: Retain the original definition i.e., “Sodium Ascorbate contains NLT 99.0% and NMT 101.0% of sodium ascorbate (C₆H₇NaO₆), calculated on the dried basis.”

EC-Initiated change #2: In the *Assay* section, remove the “*Content of Ascorbate*” title and revise the formula to calculate Sodium Ascorbate

EC-Initiated change #3: In the *Assay* section, move the “*Content of Sodium*” test to Other Components section

EC-Initiated change #4: In the *Assay* section, delete the *Content of Sodium Ascorbate* test

Monograph/Section(s): Sodium Iodide I 123 Solution /Multiple Sections

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment summary #1: The commenter indicated that omission of the *Sodium Iodide I 123 Solution* monograph will have an impact on the *Sodium Iodide I 123 Capsules* monograph as some of the tests are cross-referenced in the Capsules monograph.

Response: Comment incorporated. The *Sodium Iodide I 123 Capsules* monograph is updated to include procedure details from the *Sodium Iodide I 123 Solution* monograph to resolve the cross-reference issue.

Monograph/Section(s): Sodium Nitrite / Multiple Sections

Expert Committee: Small Molecules Monograph 2

No. of Commenters: 0

EC-Initiated Change #1: In the test for *Limit of Aluminum, Iron and Selenium*, the unit for the weight of the sample taken was corrected to g so that the result is ppm (w/w).

EC-Initiated Change #2: In the test for *Limit of Calcium and Potassium*, the unit for the weight of the sample taken was corrected to g so that the result is ppm (w/w).

Monograph/Section(s): Sodium Picosulfate / Organic Impurities

Expert Committee: Small Molecules 3

No. of Commenters: 1

Comment summary #1: The commenter recommended removing the reporting threshold from the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to do further stakeholder engagement.

Monograph/Section(s): Triazolam Tablets / Organic Impurities

Expert Committee: Small Molecules 4

No. of Commenters: 1

Comment summary #1: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from

monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

Comment summary #2: The commenter recommended revising the impurity profile and acceptance criteria for total degradation products to be consistent with what has been approved.

Response: Comment not incorporated. The Expert Committee will consider future revisions to this monograph upon receipt of supporting information.

Monograph/Section(s): Triclabendazole / Multiple Sections

Expert Committee: Small Molecules 1

No. of Commenters: 1

Comment Summary #1: The commenter recommended removing the reporting threshold in the test for *Organic Impurities* as it will vary based on product-specific factors.

Response: Comment not incorporated. Based on comments received on a proposed policy for reporting thresholds, USP determined that the issue of the removal of reporting thresholds from monographs needs further stakeholder engagement. USP intends to conduct further stakeholder engagement.

EC-Initiated Change #1: The Expert Committee updated the chemical name for Triclabendazole Related Compound B in the *USP Reference Standards <11>* section from 5-Chloro-6-(2,3-dichlorophenoxy)-1*H*-benzimidazole-2-thiol to (5-Chloro-6-(2,3-dichlorophenoxy)-1,3-dihydro-2*H*-benzimidazole-2-thione) to be consistent with the reference standard certificate and CAS number associated with the material.

Monograph/Sections: Zinc Chloride / Assay

Expert Committee: Small Molecules 3

No. of Commenters: 1

Comment summary #1: The commenter indicated that the lower limit for the Assay was different from what has been approved.

Response: Comment incorporated. The *Acceptance criteria* for the Assay was updated from “NLT 98.0% and NMT 102.0%” to “NLT 97.0% and NMT 102.0%” to be consistent with FDA-approved specifications.